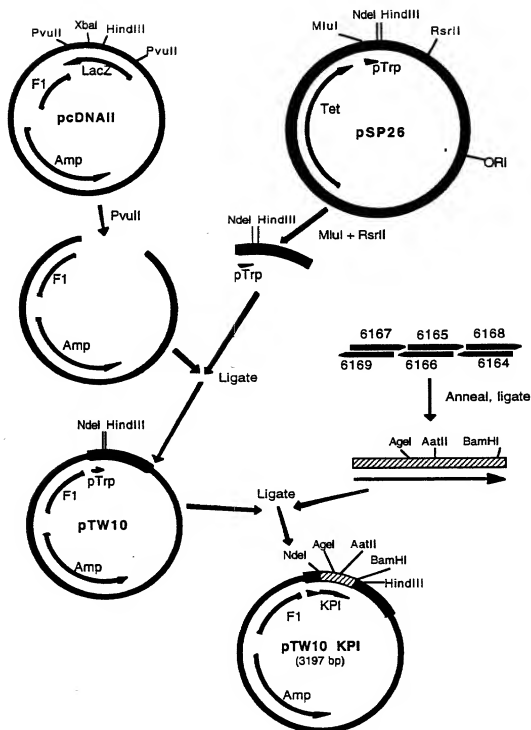


Figure 1



10076504.021902

Title: PROTEASE INHIBITOR
PEPTIDES

Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 2

NdeI

TATG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCT GTG ACA AAA
AC TTT GTT TCG TGA TAA CGT GAC CGT GAG AAT GGC AAT GAC AAA TGG GGA CAC TGT TTT
►Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI

Agel

GCG GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG
CGG CTC CAC ACG AGA CTT GTT CGA CTC TGG CCA GGC ACG GCA CGT TAC TAG AGG GCG ACC
►Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Met Ile Ser Arg Trp

AatII

TAC TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC
ATG AAA CTG CAG TGA CTT CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG
►Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

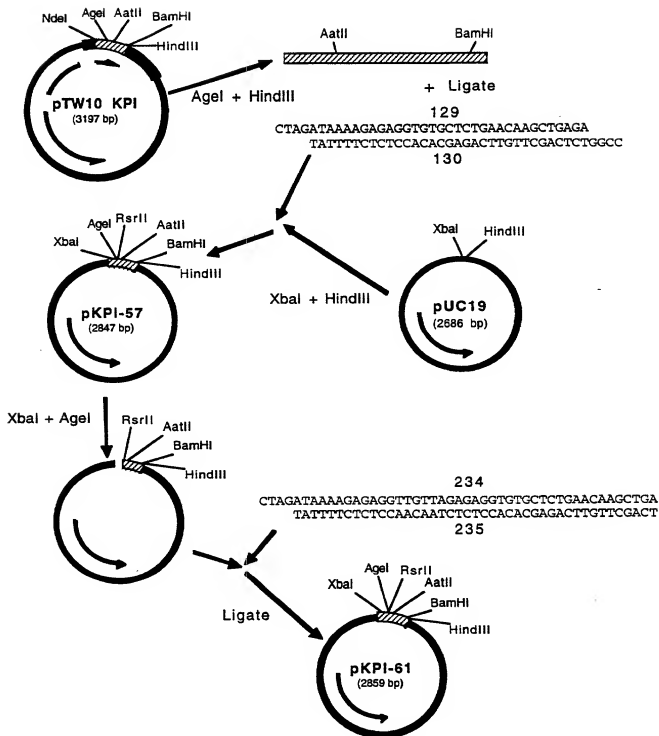
BamHI

HindIII

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TA
GCA TTG TTG AAA CTG TGA CTT CTC ATG ACG TAC CGT CAC ACG CGT AGG CGA TAA ATT CGA
►Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076604.021902

Figure 3



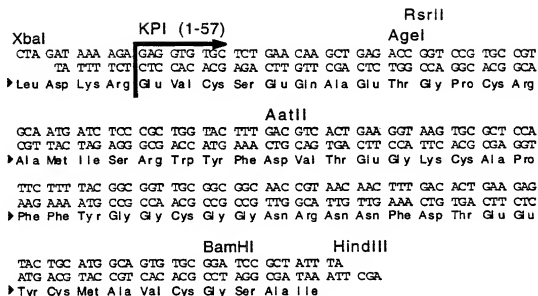
10075604.021902

Title: PROTEASE INHIBITOR
PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 09/201,715

Figure 4



1075604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

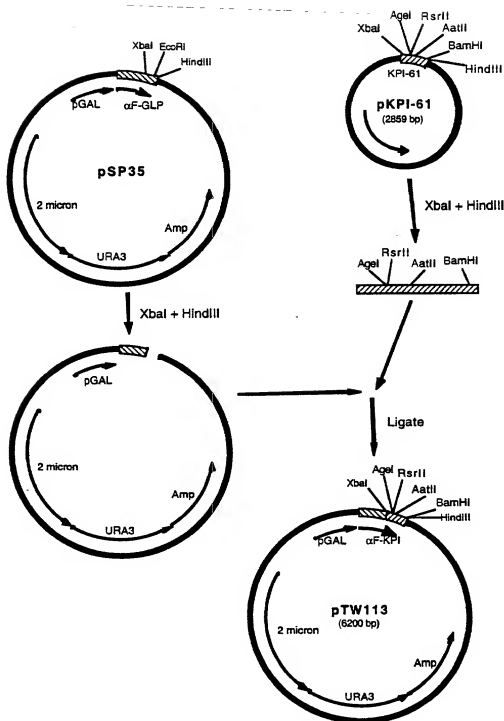
Figure 5

KPI (-4-57)

XbaI	<div style="display: flex; align-items: center; justify-content: center;"> <div style="border-left: 1px solid black; padding-left: 5px; margin-right: 5px;">GAG</div> <div style="border-bottom: 1px solid black; width: 100px; position: relative;"> <div style="position: absolute; top: -10px; left: 50%; transform: translateX(-50%);">→</div> </div> </div>	RsrII
	<div style="display: flex; justify-content: space-between;"> CTA GAT AAA AGA GAG GGT GTT AGA GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT Agel </div> <div style="display: flex; justify-content: space-between;"> TA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT CGA CTC TGG CCA </div>	
	<div style="display: flex; justify-content: space-between;"> ▶ Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln Ala Glu Thr Gly </div>	
AatII		
	<div style="display: flex; justify-content: space-between;"> CCG TGC CGT GCA ATG ATC TCC CGC TGG TAC TTT GAC GTC ACT GAA GGT AAG TGC </div> <div style="display: flex; justify-content: space-between;"> GGC ACG GCA CGT TAC TAG AGG GCG ACC ATG AAA CTG CAG TGA CTT CCA TTC ACG </div>	
	<div style="display: flex; justify-content: space-between;"> ▶ Pro Cys Arg Ala Met Ile Ser Arg Trp Tyr Phe Asp Val Thr Glu Gly Lys Cys </div>	
BamHI HindIII		
	<div style="display: flex; justify-content: space-between;"> GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TA </div> <div style="display: flex; justify-content: space-between;"> CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA </div>	
	<div style="display: flex; justify-content: space-between;"> ▶ Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile </div>	

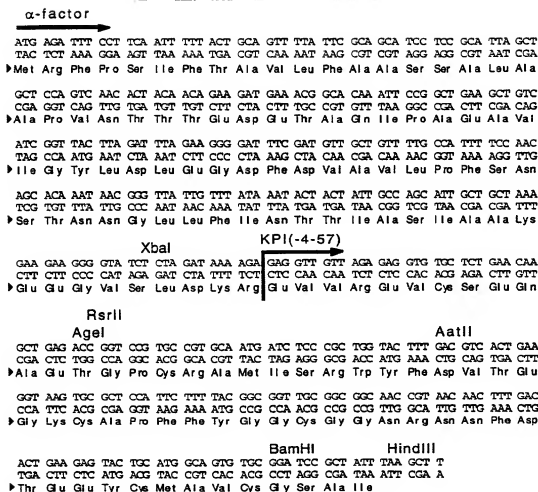
10076604.021902

Figure 6



10076604.021902

Figure 7



10076504.021902

Title: PROTEASE INHIBITOR
PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 09/201,715

Figure8

KPI(-4-57)

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - Ile - Ser - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

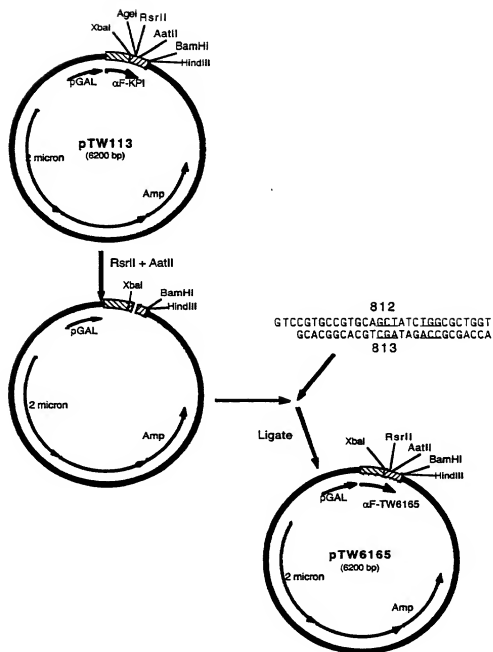
Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10076604.021902

Figure 9



10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES

Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 10

pTW 6165

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TGG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA AAG GCT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CCG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A; S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TGG CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT CCA TAG ACC GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 11

812	GTCCGTGCCGTGCAGCTATCTGGCGCTGGTACTTTGACGT	pTW6165 KPI(-4-57; M15A, S17F)
813	GCACGGCACGTCTGATAGACCGGACCATGAAAC	
814	GTCCGTGCCGTGCAGCTATCTACCGCTGGTACTTTGACGT	pTW6166 KPI(-4-57; M15A, S17Y)
815	GCACGGCACGTCTGATAGATGGCGACCATGAAAC	
867	GTCCGTGCCGTGCATTTGATCTTCCGCTGGTACTTTGACGT	pTW6175 KPI(-4-57; M15L, S17F)
868	GCACGGCACGTAACTAGAAAGGCGACCATGAAAC	
1493	GTCCGTGCCGTGCATTTGATCTACCGCTGGTACTTTGACGT	pBG028 KPI(-4-57; M15L, S17Y)
1494	GCACGGCACGTAACTAGATGGCGACCATGAAAC	
925	GTCCGTGCCGTGCAATGCACITCCGCTGGTACTTTGACGT	pTW6183 KPI(-4-57; I16H, S17F)
926	GCACGGCACGTTACGTGAAGGCGACCATGAAAC	
927	GTCCGTGCCGTGCAATGCACITACCGCTGGTACTTTGACGT	pTW6184 KPI(-4-57; I16H, S17Y)
928	GCACGGCACGTTACGTGATGGCGACCATGAAAC	
929	GTCCGTGCCGTGCAATGCACITGGCGCTGGTACTTTGACGT	pTW6185 KPI(-4-57; I16H, S17W)
930	GCACGGCACGTTACGTGACCGCGACCATGAAAC	
863	GTCCGTGCCGTGCAGCTCACTCCCGCTGGTACTTTGACGT	pTW6173 KPI(-4-57; M15A, I16H)
864	GCACGGCACGTCTGATGAGGGCGACCATGAAAC	
865	GTCCGTGCCGTGCATTTGCACTCCCGCTGGTACTTTGACGT	pTW6174 KPI(-4-57; M15L, I16H)
866	GCACGGCACGTAACTGAGGGCGACCATGAAAC	

10075604-021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 12

PTW 6166

α -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TAC CCG TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ATG CCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Tyr Arg Trp Tyr Phe Asp Val Thr Glu
GCT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG CCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

1076604-021697

Figure 13

pTW 6175

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT GCA CAG
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT CCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CCG TCG TAA CGA CGA TTT
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15L, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT
▶ Ala Glu Thr Gly Pro Cys Arg Ala Leu Ile Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CGG TTG GCA TTG TTG AAA CTG
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076604.021902

Figure 14

pBG028

α -factor

ATG AGA TTT CTT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG COT COT AGG AGG CGT AAT CGA
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC COT GTT TAA GGC CGA CTT CGA CAG
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15L, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TAC CCG TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT
▶ Ala Glu Thr Gly Pro Cys Arg Ala Leu Ile Tyr Arg Trp Tyr Phe Asp Val Thr Glu
GCT AAG TCC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC COT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT ACG CGA TAA ATT CGA A
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076604-021902

Figure 15

pTW6183

α -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
▶Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TCC CGT GTT TAA GGC CGA CTT CCA CAG
▶Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
▶Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
▶Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; I16H, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TCC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
▶Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TTC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG AAG GCG ACC ATG AAA CTG CAG TGA CTT
▶Ala Glu Thr Gly Pro Cys Arg Ala Met His Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
▶Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
▶Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076604.021902

Figure 16

pTW6184

α -factor

ATG AGA TTT GGT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
▶Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CGG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
▶Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Gu Ala Val
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
▶Ile Gly Tyr Leu Asp Leu Gu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
▶Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; I16H, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
▶Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Gu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TAC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTC ATG CGC ACC ATG AAA CTG CAG TGA CTT
▶Ala Glu Thr Gly Pro Cys Arg Ala Met His Tyr Arg Trp Tyr Phe Asp Val Thr Gu
GCT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CGC CGT TTG GCA TTG TTG AAA CTG
▶Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT ACG CGA TAA ATT CGA A
▶Thr Gu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076604-021902

Figure 17

pTW6185

α-factor

ATG AGA TTT GCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GPT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TGG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; I16H, S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TGG CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT TAC GAG ACC GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Met His Trp Arg Trp Tyr Phe Asp Val Thr Glu
GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GCA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

1076604.021902

Figure 18

pTW6173

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
▶Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA CTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
▶Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
▶Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CCG TCG TAA CGA CGA TTT
▶Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A, I16H)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
▶Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CTT GCA GCT CAC TCC CAC TGG TAC TTT GAC CTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CTT CCA GTC AGG CCG ACC ATG AAA CTG CAG TGA CTT
▶Ala Glu Thr Gly Pro Cys Arg Ala Ala His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
▶Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG CCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CTT CAC ACG CCT AGG CGA TAA ATT CGA A
▶Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076504.021907

Figure 19

pTW6174

α -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT TTA AAT ACT ACT ATT GGC AGC ATT GCT GCT AAA
TGG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CCG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15L, I16H)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT AAC GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Leu His Ser Arg Trp Ty Phe Asp Val Thr Glu

GCT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 20

KPI(-4-57; M15A, S17W) TW6165

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - Ile - Trp - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 21

KPI (-4-57; M15A, S17Y) TW6166

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - Ile - Tyr - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10076604.021902

Figure 22

KPI(-4-57; M15L, S17F) TW6175

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Leu - Ile - Phe - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

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200720-1089001

Figure 23

KPI(-4-57; M15L, S17Y) BG028

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Leu - Ile - Tyr - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 24

KPI(-4-57; I16H, S17F) TW6183

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - His - Phe - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 25

KPI(-4-57; I16H, S17Y) TW6184

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - His - Tyr - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 26

KPI(-4-57; I16H, S17W) TW6185

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - ~~His~~ - ~~Trp~~ - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10075604.021001

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Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 27

KPI(-4-57; M15A, S17F) DD185

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - Ile - Phe - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10076604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 28

KPI(-4-57; M15A, I16H) TW6173

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - His - SerTrp - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

10075604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 29

KPI(-4-57; M15L, I16H) TW6174

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - ~~Leu~~ - ~~His~~ - Ser - Arg
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile
52 53 54 55 56 57

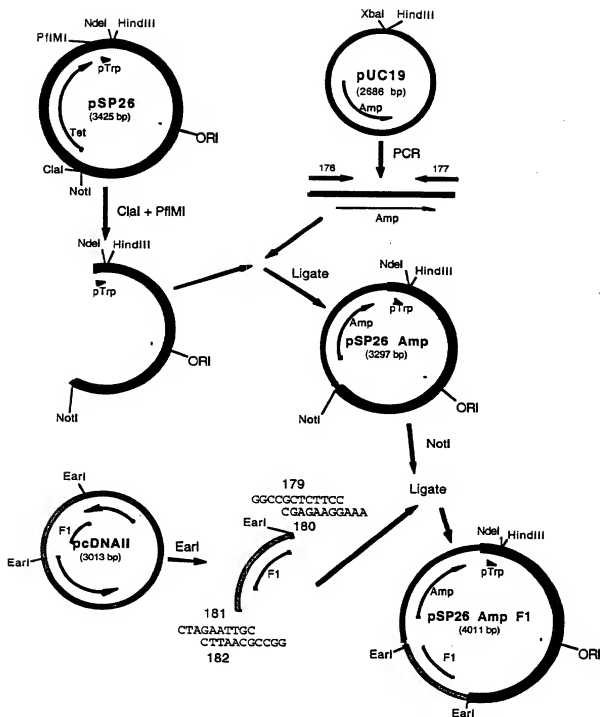
10076804.021902

Title: PROTEASE INHIBITOR
PEPTIDES

Inventor(s): R. Tyler WHITE et al.

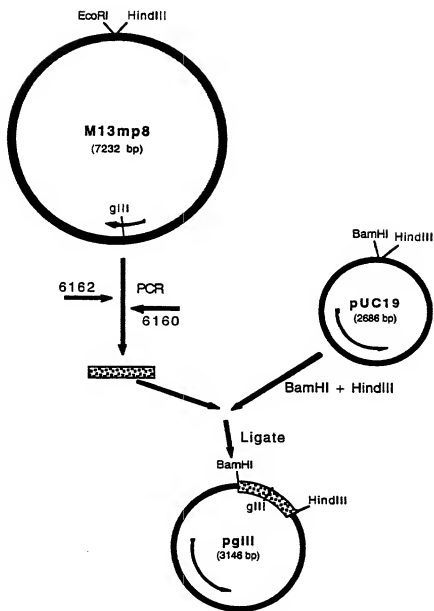
Appl. No.: 09/201,715

Figure 30



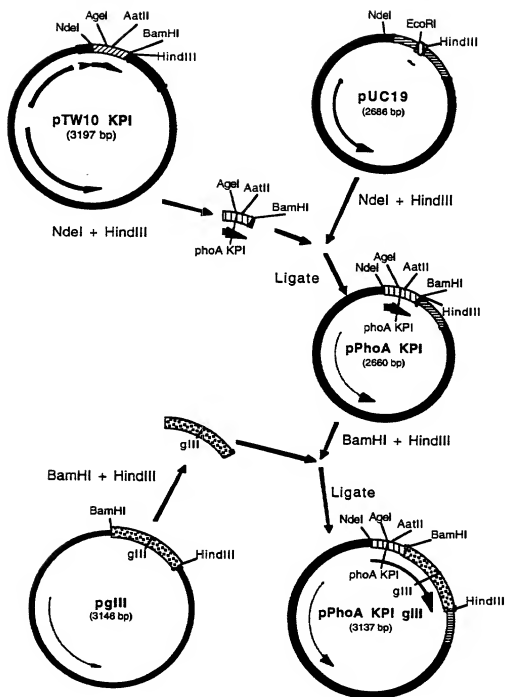
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Figure 31



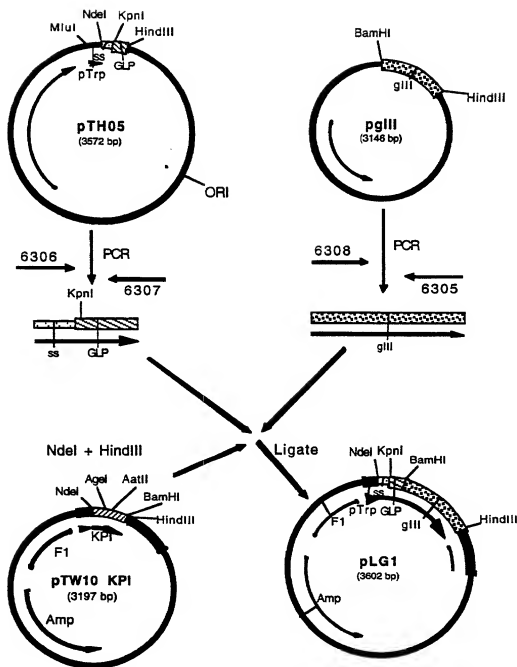
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Figure 32



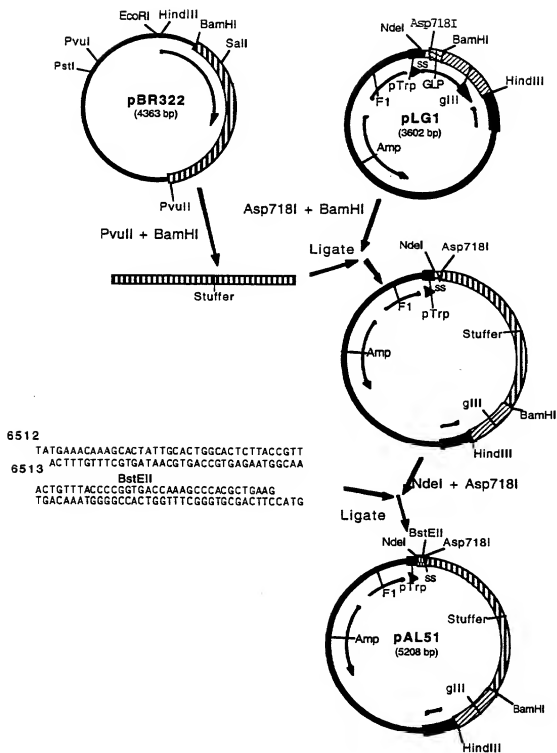
10076604.021900

Figure 33



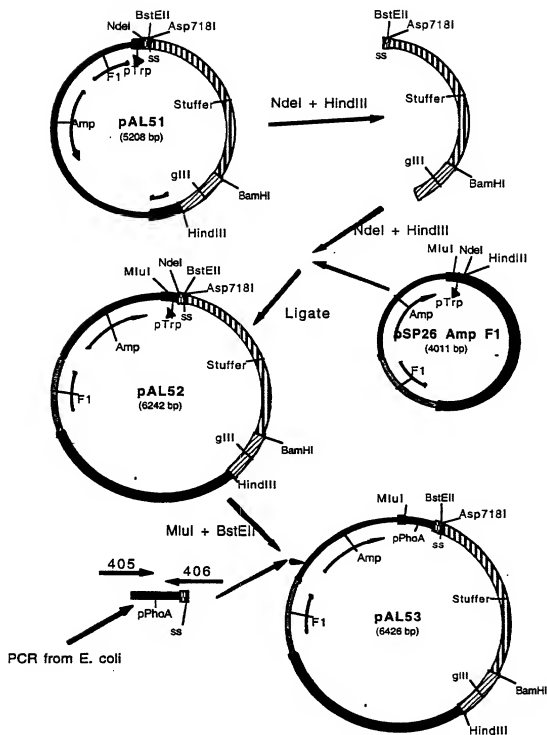
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Figure 34



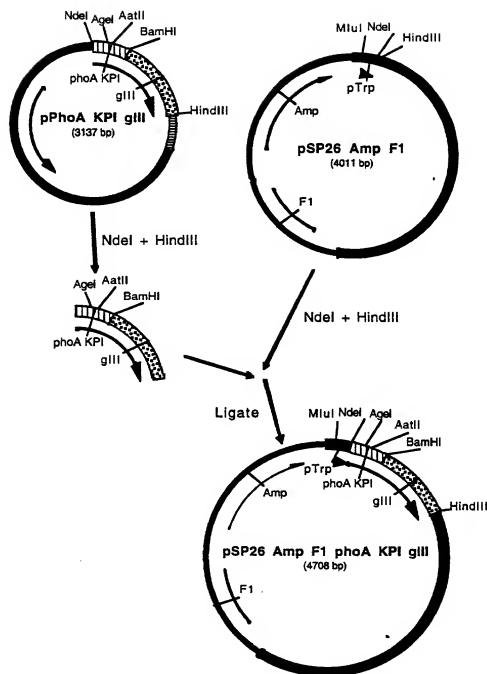
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Figure 35



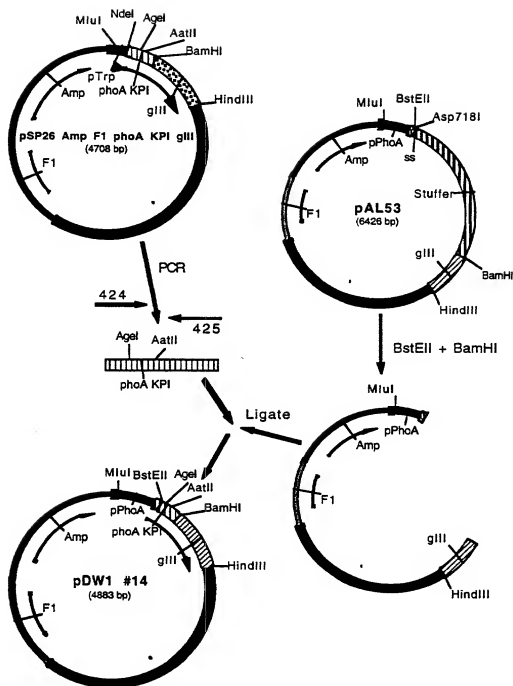
10076604.021902

Figure 36



10076604.021902

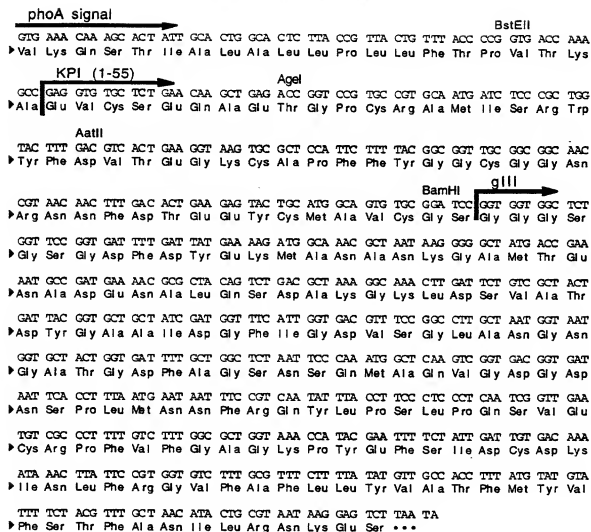
Figure 37



10076604-021902

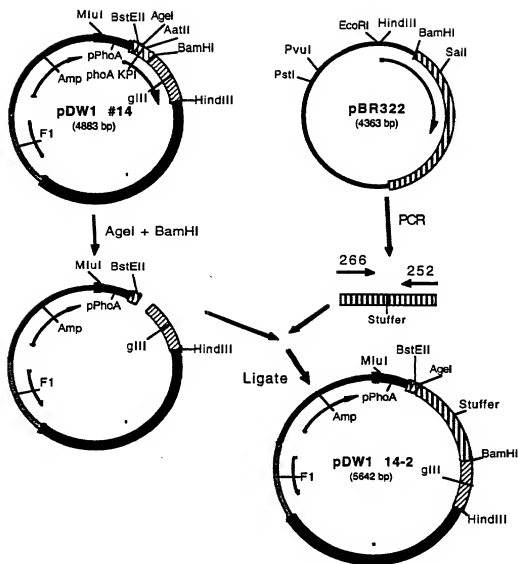
Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 38



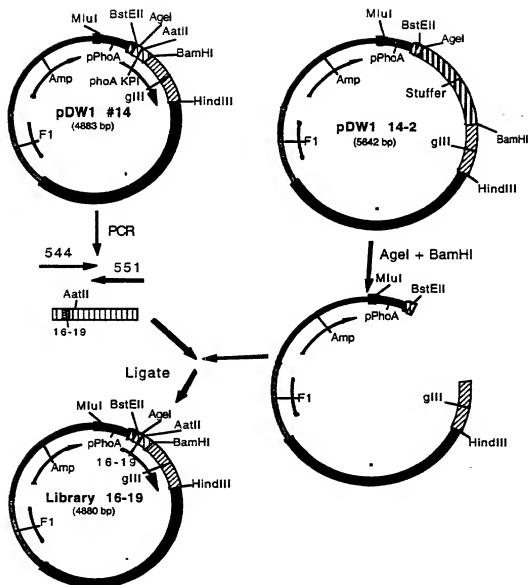
10076604.021902

Figure 39



10076604.021902

Figure 40



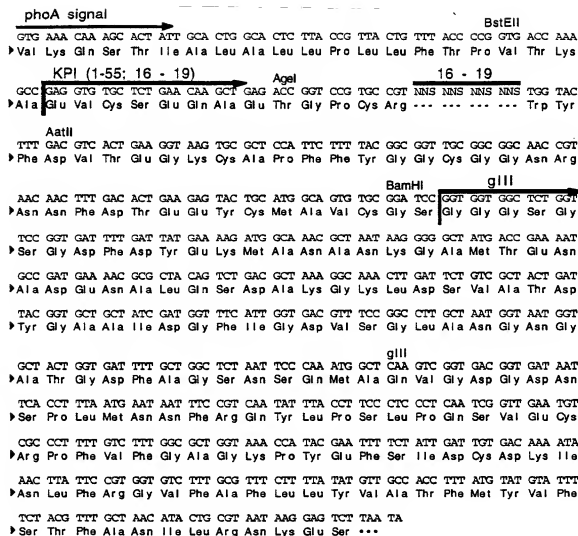
10076604.021902

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PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 09/201,715

Figure 41



10075604.021902

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 09/201,715

Figure 42

phoA signal →

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA
 ▶ Val Lys Glu Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55; M15A, S17F) →

GCG GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTT CCG TGG
 ▶ Ala Glu Val Cys Ser Glu Glu Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Phe Arg Trp

Agel

AatII

TAC TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC
 ▶ Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

BamHI

gIII

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT
 ▶ Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser

Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT
 ▶ Asn Ala Asp Glu Asn Ala Leu Glu Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT
 ▶ Asp Tyr Gly Ala Ala Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT
 ▶ Gly Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Glu Met Ala Glu Val Gly Asp Gly Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA
 ▶ Asn Ser Pro Leu Met Asn Asn Phe Arg Glu Tyr Leu Pro Ser Leu Pro Glu Ser Val Glu

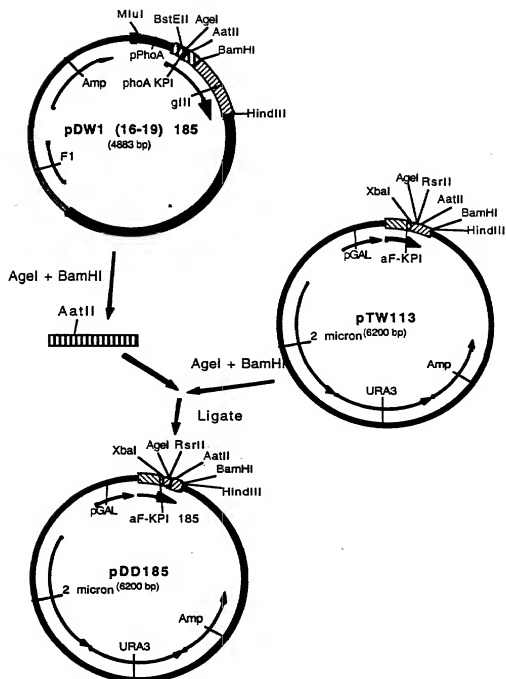
TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA
 ▶ Cys Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys

ATA AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA
 ▶ Ile Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val

TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA
 ▶ Phe Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser

1007604-021902

Figure 43



10076604.021902

Title: PROTEASE INHIBITOR

PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 09/201,715

Figure 44

pDD185

 α -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
 TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
 ▶Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
 CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
 ▶Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
 TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
 ▶Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
 TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
 ▶Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TCC TCT GAA CAA
 CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
 ▶Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA
 CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT
 ▶Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TCC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
 CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
 ▶Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
 TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
 ▶Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

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Figure 45

Plasma kallikrein inhibition by KPI (-4-57) variants

Variant		Substitution			K _i (nM)
		15	16	17	
TW113	KPI (-4-57)				45.00
DD185	KPI (-4-57; M15A, S17F)	A		F	0.39
TW6165	KPI (-4-57; M15A, S17W)	A		W	0.65
TW6166	KPI (-4-57; M15A, S17Y)	A		Y	0.40
TW6175	KPI (-4-57; M15L, S17F)	L		F	0.50
BG028	KPI (-4-57; M15L, S17Y)	L		Y	1.10
TW6183	KPI (-4-57; I16H, S17F)		H	F	1.20
TW6184	KPI (-4-57; I16H, S17Y)		H	Y	0.91
TW6185	KPI (-4-57; I16H, S17W)		H	W	1.30
TW6173	KPI (-4-57; M15A, I16H)	A	H		1.00
TW6174	KPI (-4-57; M15L, I16H)	L	H		0.90

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FIGURE 46A

Variant	Sequence	Inhibition Ki (nM)		
		kalikreil	Plasmin	Xa
Aprotinin	RPDFCLEPPYTPGPKARIIIRVFNNAKAGLQTFYVYGCGRAKNNFNKSAEDCHRTGGAA	20.00	0.23	5000.0
Aprotinin R15, S42	DFCLEPPYTPGPKARIIIRVFNNAKAGLQTFYVYGCGRAKNNFNKSAEDCHRTGGAA	0.91	0.17	3983.0
KPI (-4-57)	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	45.00	34.00	3718.0
TW6167	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	61.00	34.00	3641.0
BG031	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	49.00	34.00	498.0
BG032	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	34.00	34.00	731.0
TW101	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	2000.00	11.50	369.0
TW6208	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	560.00	3.70	1600.0
TW106	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	1.70	11.20	1600.0
DD108	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	9.50	2.10	1681.0
DD109	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	2.10	6.24	421.0
DD110	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	5.60	6.24	55.0
DD111	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	6.80	9.98	998.0
DD112	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	78.00	368.0	368.0
TW6179	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	4.70	103.58	4532.0
TW6163	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	315.00	70.00	885.0
TW6172	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	150.00	1514.0	1514.0
TW6180	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	38.00	10.00	489.0
TW6181	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	145.00	89.00	806.0
BG001	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	16.00	315.0	315.0
TW116	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	17.00	2128.0	110.0
DD102	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	15.00	237.0	345.0
DD103	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	18.00	198.0	320.0
DD104	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	25.80	3521.0	395.0
DD105	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	36.00	752.0	752.0
TW6168	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	70.83	277.0	277.0
TW6182	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	54.00	8960.0	133.0
TW6194	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI	110.20	40.0	116.0
TW6210	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI			
CL006	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI			
BG012	EVVREVCSQAETGPPCHRAHISRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEXCHAVCGSAI			

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FIGURE 46B

TW6209	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	81.00	45.90	184.0	613.0
TW6211	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	184.00		402.0	
DD128	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	44.00			37.0
TW6142	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	18.00	18.00	7972.0	225.0
AL301	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	216.00		1557.0	
AL302	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	39.00			316.0
TW6147	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	35.00		1090.0	179.0
TW6138	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	18.00		921.0	309.0
TW6135	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	11.00		915.0	39.0
TW6156	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	11.00		475.0	27.0
TW6140	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	35.00			
TW6157	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	42.00			
TW6141	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	6.00	24.00	13009.0	68.0
TW118	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	15.00			
DD100	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	40.00		511.0	168.0
TW6158	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	29.00			
TW6159	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	17.00			64.0
TW6161	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	7.50	18.00	1507.0	8.7
DD101	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	64.00		924.0	
TW6151	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	163.00		1162.0	954.0
TW6139	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	19.00	22.80	152.0	78.0
TW6153	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	11.20	21.30	65.0	36.0
TW122	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	32.00	27.00		581.0
TW6178	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	16.00		444.0	
TW6148	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	40.00			
TW124	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	64.00	48.00		
TW6149	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	54.00			
TW6173	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	1.00	7.24	1432.0	
TW6174	EVVREVCSEQLGTPGCRAMISRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	0.96	6.89	2796.0	
BG002	EVVREVCSEQLGTPGCRALLSRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	0.98	19.00	403.0	60.0
DD129	EVVREVCSEQLGTPGCRALLSRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	3.60		1864.0	6.0
DD185	EVVREVCSEQLGTPGCRATIRWYFDVTBKGKAPFFYGGCGGNRRNFDTEYCHAVOGSSAI	0.39	8.71	150.0	196.0

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FIGURE 46C

TW6165	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.65	16.40	206.0	
TW6166	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.4	10.10	73.0	
BG028	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	1.10	12.10	93.8	
TW6169	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	1.20		619.0	111.0
DD113	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.85	12.80	293.0	74.0
TW6175	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.50	7.46	35.0	56.0
TW6201	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	34.60		419.0	
TW6202	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	128.50		1377.0	
TW6204	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	31.20		5045.0	
TW6205	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI			147.0	87.0
DD114	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.70	7.77	224.0	
TW6190	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.83	52.20	589.0	1396.0
TW6183	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	1.20	11.68	12440.0	159.0
TW6184	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.91	11.96	14000.0	214.0
TW6185	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	1.30	18.60	388.0	473.0
BG003	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	36.00		467.0	
TW6186	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.48	8.86	186.0	11.0
TW6187	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	3.80	15.40	92.0	15.0
TW6188	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	4.00		419.0	24.0
TW6189	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	4.00			34.0
TW6170	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	2.50		452.0	
DD115	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI			213.0	299.0
DD1170	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.99	18.00	550.0	
TW6176	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	3.50	118.00	56.0	
TW6177	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	7.20	32.70	245.0	156.0
BG006	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	0.30	12.10	80.0	
DD130	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	5.50			9.5
DD131	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	7.90	2.00	1385.0	3.3
DD132	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	112.00			16.8
DD120	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	8.30			11.0
DD121	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	19.00			21.0
BG014	EVVREVCSEQAETGFCRAAIIHRYFDVTGKCAPFFYGGCGGNRRNFDTEYCHAVCGSAI	9.20	18.70	18.0	

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FIGURE 46D

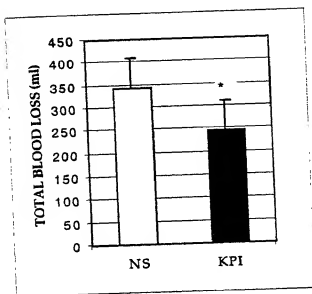
DD122	EVVREVCSEQLGPGCRALIFRWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	15.00			46.0
BG015	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	6.00	12.20	19.4	597.0
BG020	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	1.70		106.0	
BG022	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	0.64	7.26	14.5	
BG023	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	23.00		262.0	
BG024	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	4.10	7.47	38.7	
BG027	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	5.80		144.0	
DD116	EVVREVCSEQLGPGCRALIFRWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	0.14		583.0	84.0
TW6191	EVVREVCSEQLGPGCRALIFRWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	0.26		664.0	20.0
DD117	EVVREVCSEQLGPGCRALIFRWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	0.11		1034.0	99.0
BG029	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	3.20		7.9	
BG030	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	4.60		26.1	
BG033	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	0.75		5.6	
BG034	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	0.47		18.5	
BG040	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	3.40		8.6	
BG016	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	160.00		178.0	
BG017	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	180.00		200.0	
BG021	EVVREVCSEQLGPGCRGSIIRHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	140.00		224.0	
BG025	EVVREVCSEQLGPGCLIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	65.00		16.2	
BG026	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	50.00		34.9	
DD118	EVVREVCSEQLGPGCRALIIHWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	0.53			
DD134	EVVREVCSEQLGPGCRALIFRWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	1.10	1.05	15640.0	0.6
DD135	EVVREVCSEQLGPGCRALIFRWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	1.30		7473.0	0.9
DD136	EVVREVCSEQLGPGCRALIFRWYFDVTGKCAPFFYGGCGGNNRNFDTTEYCHAVCGSAI	1.10			1.8

Figure 47

VOLUMES

NS	344.25
KPI	245.75

	KPI	NS
	298	366
	266	342
	354	294
	258	385
	168	288
	266	469
	172	338
	184	272
MEAN	245.75	344.25
STDEV	66.2414415	63.97488346
TTEST	0.009094999	



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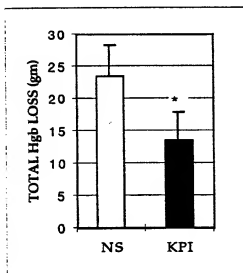
Figure 48

HEMOGLOBIN

NS	23.61
KPI	13.59

	KPI	NS
	16.58	24.95
	15.19	24.87
	20.21	20.46
	8.99	27.59
	14.63	18.23
	15.31	31.59
	7.7	23.26
	10.14	17.96

MEAN	13.59375	23.61375
STDEV	4.261438	4.68761
TTEST		0.000536



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Figure 49

PaO₂

	Baseline PaO ₂		End CPB		Obs 60 min		Obs 180 min	
	KPI	NS	KPI	NS	KPI	NS	KPI	NS
	652.2	670.9	495.7	60.5	483.7	441.3		391.3
	654	559.2	444.6	132.2	330.1	448.7	264.1	484.6
	596.2	622.9	170.2	93.8	415.4	85.1	416.5	81.3
	606.2	689.2	264.2	333.9	430.2	529.6	361.9	333.2
	633.1	665.1	567.2	341.7	613	568.3	90.8	546.6
	646.6	527	507.4	226.9	564.3	438.1	518.2	485.3
	563.2	461.7	547.1	89.1	501	42.6	494.2	45.6
	659.9	508	416.6	59.7	504.5	405.8	452	383.7
MEAN	626.425	588	426.625	167.225	480.275	369.938	371.1	344
STDEV	34.4692	85.5055	140.474	117.993	88.6187	196.523	150.277	186.22
	3	6	1	1	9	5	4	7
TTEST	p= 0.268		p= 0.0014		p= 0.17915		p= 0.76	
	NS.				NS.			

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Figure 50

Summary of Data

Total Volume loss		Total High Loss	
KPI-1	298	16.58	
KPI-2	266	15.19	
KPI-3	354	20.21	
KPI-4	258	8.99	
KPI-5	168	14.63	
KPI-6	266	15.31	
KPI-7	172	7.7	
KPI-8	184	10.14	
MEAN	245.75	13.59	
STDEV	66.24	4.26	

NS-1A	366	24.95	
NS-2	342	24.87	
NS-3	294	20.46	
NS-4	385	27.59	
NS-5	288	18.23	
NS-6	469	31.59	
NS-7	338	23.26	
NS-8	272	17.96	
MEAN	344.25	23.61	
STDEV	63.97	4.69	

$p = 0.009$ $p = 0.0005$

Total Volumes		Serial Chest tube Hbg			
Chest tube	Sacrifice	0-30min	30-60min	60-120min	120-180min
185	113	3.7	4.3	8.6	6.2
198	68	4.3	6.4	6.7	5.7
142	212	4.1	4.4	7	7.1
190	68	2.8	4	4.4	1.9
96	72	6.3	6.5	7	6.7
188	78	4.1	6.1	5.6	6.3
134	38	3.1	4.6	5.4	4.4
158	26	6.9	5.8	5.4	4.2
MEAN		4.41	5.26	6.26	5.3
STDEV		1.45	1.04	1.32	1.72

274	92	7.7	8.6	6.1	5.4
236	106	7.2	7.4	7.6	7.1
252	42	5.4	7.5	7.5	6.5
303	82	8.4	7.2	7.1	6.3
140	148	7.5	7.2	5.2	5.6
261	208	4	7	7.3	7.4
218	120	7.5	7.7	5.8	4.2
206	66	7.4	8.2	6	5.3
MEAN		6.89	7.6	6.58	6.1
STDEV		1.44	1.04	0.91	0.85

$p = 0.004$ $p = 0.002$ NS NS